

THE IMPORTANCE OF THE TREATMENT OF PERNICIOUS ANEMIA ON A QUANTITATIVE BASIS.

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Pernicious anemia has been demonstrated by Castle and his associates¹ to be a disorder which they have considered a "conditioned deficiency" disease to indicate that the deficiency syndrome is the result not of a deficient diet, but a deficient utilization of a normal diet owing to a specific defect in the afflicted individual. They have shown that these patients in relapse lack an "intrinsic factor" secreted by the normal stomach, which when properly brought in contact with an "extrinsic factor," namely, appropriate food, causes material to be formed which is necessary for normal blood production. Like all deficiency disorders, whether due to a lack of a hormone, a vitamin, a mineral, or other substances, treatment must consist in supplying the deficient factor on a quantitative basis.

In pernicious anemia the degree of deficiency will vary according to:

1. The degree of deficiency of the intrinsic factor (complete or partial).
2. The amount of extrinsic factor ingested.
3. The ability of the gastrointestinal tract to absorb potent material. (Perhaps the state of the gastrointestinal contents may be such as to enhance destruction of potent material entering the body by this route.)
4. The ability to utilize or metabolize the potent substance after it enters the blood stream.
5. The occurrence and severity of inhibitory factors, such as infection, arteriosclerosis, and damage to important organs.
6. The loss of blood building material from the body, as from blood loss and pregnancy.

7. The amount of potent material stored in the body.

If the deficiency is slight, much less material will be required to restore equilibrium than when it is severe. If the body has difficulty in obtaining material from the gastrointestinal tract, a relatively small amount of material given parenterally, may adequately supply the need of the body. The degree of deficiency, however, may be independent of the ease with which the material enters the body by nature's route so that one case may require more active principle parenterally than another. The treatment of pernicious anemia is not by liver, kidney, stomach, brain, pancreas, placenta, or preparations of these organs, but by enough potent material irrespective of its source for the given individual case, which implies that the substance must enter the body and not simply enter the gastrointestinal tract. The prescription of arbitrary amounts leads to unnecessary illness. The patient's body must always have enough of a given substance to maintain the best health, not better health, and to prevent the progress or development of any symptoms or abnormal signs. Cases which have not done well have been reported as treated with what were called "satisfactory" or "optimal" amounts of material, but it is evident that although many of these patients had relatively large amounts of material by mouth they have by no manner of means had a true optimal quantity or a large enough amount to benefit adequately their individual cases. Even so, amounts may be stated that will be found great enough to induce remissions and maintain health in the usual uncomplicated case of pernicious anemia in an individual under 50 years of age; for example, daily by mouth 250 grams of liver pulp or liver extract No. 343 (N.N.R.) derived from 400 grams of liver or extract for intramuscular use, as prepared by Castle et al.,² from 5 to 10 grams of liver (1 to 2 c.c. of solution). It must be appreciated, however, that cases vary widely in the degree of deficiency and the effects of inhibitory factors upon them. Thus, very different amounts will be required by different cases so that relatively rarely quantities much greater than those stated will have little or no effect by mouth and occasionally distinctly greater amounts are necessary when given intramuscularly.

At present there is no satisfactory way to define a unit of potent material and this has caused confusion concerning the com-

parative potency of organs and the many sorts of extracts made from them. By determining the amount of material just sufficient to produce a maximal reticulocyte response in uncomplicated cases, an approximation can be made to the potency of the preparations. As a requisite to the adequate treatment of pernicious anemia, one must know what a given amount of the preparation to be used may be expected to accomplish under usual conditions. When extracts are made there is a very considerable loss of potent material, so that the most satisfactory alcohol precipitated liver extracts of the type described as fraction G³ and commercially available under various names, such as liver extract No. 343 (N.N.R) derived from 100 grams of liver, are equivalent in potency to about 65 grams of liver prepared for ingestion. The purer the potent material has been rendered, the greater the loss of active principle. Material effective parenterally in doses of about 0.025 gram daily, has been made from about 6000 grams of liver, but the relatively crude fraction G preparation is effective parenterally in daily doses of about 0.4 gram derived from 10 grams of liver. It is evident that there is no practical advantage in utilizing a product purer than fraction G. A relatively crude extract such as fraction G is at least 30 times as potent when given intramuscularly as when given by mouth. This very significant fact is to be recognized, for among other reasons it indicates that there is now no reason why any patient cannot receive enough material for his given case, no matter how large an amount he may require.

The following concepts concerning the effect of the quantity of potent material should be borne in mind during the treatment of any case.

1. The treatment should not consist of supplying simply enough material to remove one symptom, such as anemia, but enough to supply indefinitely all demands for the potent material and to fill the body adequately with stores or a reserve supply of the substance.
2. A reticulocyte response may be induced with much less potent material than is required for a maximal response. When a sub-maximal response occurs, there may be no significant increase in the concentration of the red blood cells or hemoglobin.
3. If the circumstances are comparable, more material is re-

quired to make many cells than a few cells. Thus in a patient who has had a severe relapse a greater amount of potent substance must be given daily to maintain the red blood cells at a level of 5 million than at 2 million per cubic millimeter, and it will require more material to increase their concentration from high than low levels. It should not be forgotten that the rate of increase of the cells in the peripheral blood becomes slower as their numbers increase. If a patient has had only a very mild relapse (no spinal cord symptoms and red blood cell count above 4 million per cubic millimeter) the administration of a little active principle may be sufficient to maintain a normal blood, for the deficient state may be slight. This is in contrast to a severe deficient state that can exist in a patient who has experienced a severe relapse with nerve lesions and who must be given much more potent material to maintain a normal blood and the best health possible. The exact quantitative relationships between the amount of material necessary to maintain one or another red blood cell level, or to increase the cell concentration from different levels, have not been determined. It may be said, however, that if other conditions are equal, it will often take twice as much material to maintain the red blood cells at 5 million than at 3 million per cubic millimeter, or to increase them 1 million from a level of 4 million than from a level of 1 million per cubic millimeter, and when inhibitory factors are operative greater differences may occur.

Figure 1 illustrates the course taken by the red blood cells in a patient 64 years of age, over a period of about seven years when he took various amounts of potent material. It shows the importance of the treatment of pernicious anemia on a quantitative basis.

4. The rate of red blood cell formation will vary up to a maximum with the amount of potent material administered. When the concentration of the cells is less than 2 million per cubic millimeter, usually about 150 grams of liver or liver extract No. 343 (N.N.R) derived from about 250 grams of liver, given daily, will cause the red blood cell concentration to increase by about 1.3 million per cubic millimeter in a month. If double either of these quantities are given to comparable cases, then usually the concentration increases by about 2.5 million cells in 30 days, or about as fast as it is possible for these elements to be manufactured. It must be remembered

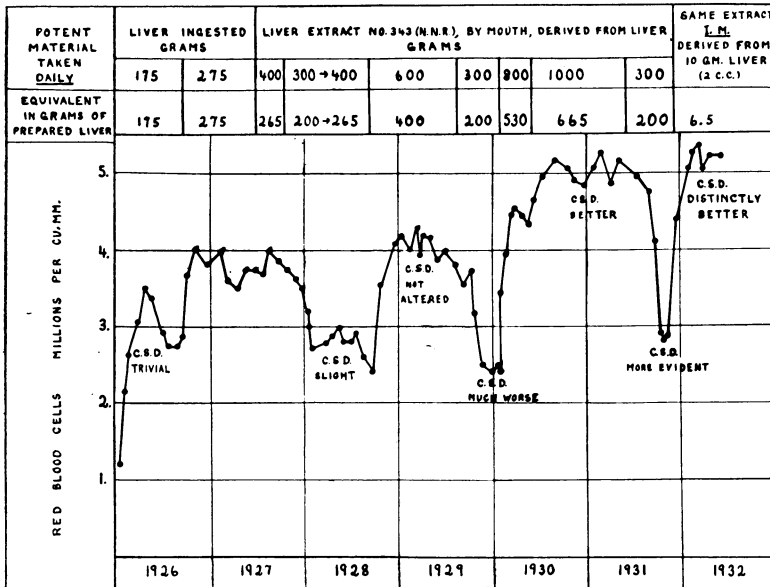


FIGURE 1.

The relation of the quantity of potent material given to the red blood cell level in a man 64 years with pernicious anemia requiring more potent material by mouth than is usual.

Note the slight overcompensation effect in the first part of 1926 and the inability to maintain the red blood cell level reached during late 1926 and in 1927 on the amount of potent material taken. The record shows that it required about twice and three times as much potent material to maintain the red blood cells at about four million and five million per cu. mm. respectively than at a level somewhat below three million per cu. mm.

The effect of small amounts of material given intramuscularly (I.M.) is also shown, suggesting the patient had difficulty in obtaining the potent substance from his gastrointestinal tract.

The development and progress of combined system disease (C.S.D.) associated with an insufficient amount of active principle is also indicated in the figure.

constantly, however, that certain cases will require very much more potent material by mouth than the usual case. Nature has a tendency to overcompensate temporarily for a defect and this may occur with liver therapy. For example, sometimes as remission proceeds the red blood cells rise well above 5 million per cubic millimeter and without alteration of the daily dose they decrease, usually slowly, to the vicinity of 5 million per cubic millimeter. Such a state of affairs

should not necessarily lead to curtailment of potent material. This over-compensatory effect is illustrated in Figure 1, during the patient's first year of treatment.

5. Probably it is possible constantly to supply enough active principle so that it is completely, or very largely, utilized in the formation of cells soon after entering the body, leaving little or none for a reserve supply to the body. If such is the case when the red blood cells have reached normal numbers and the quantity is curtailed to a theoretical maintenance dose, little or no potent material can be stored in the body to meet any slight extra demands. One must plan to fill and keep filled the assumed reservoirs of the body with potent material and not simply supply enough to maintain the cells at a normal level. Furthermore, one object in treatment is to make the blood normal in all respects and not solely the red blood cell count; the color index, cell volume and size are always for consideration.

6. The quantity of potent material needed to place the red blood cells at normal numbers does not in itself indicate that all demands of the body for the material have been met. The concept of establishing a reserve supply has been mentioned. The disease directly affects not only the hemopoietic system, but also the gastrointestinal and nervous systems. An amount of material sufficient to establish and maintain an apparently satisfactory state of the blood does not necessarily mean that enough has been given to meet the demands of other systems. Enough must be given to create great and permanent improvement in the state of the tongue and to allow nerve symptoms to decrease, and, at least, not to progress. Probably it requires much more potent material to improve or to inhibit the progress or development of nerve lesions and symptoms than it does to permit the blood constituents to be maintained at normal levels. Thus, if the body reservoirs are kept filled with an ample supply of potent material, the body should have enough to meet its demands and the development of nerve lesions need not be expected.

7. Decisions concerning maintenance doses necessitate recognition of the matters referred to above and recollection that many cases of pernicious anemia, before the days of liver therapy, would not have a relapse for six months to a year, and more, after a remis-

sion. To maintain the best possible health the body should be supplied daily with as much potent material as it utilizes daily, so that each day the body contains all that it requires for optimal nutrition. If the individual receives potent material at infrequent intervals there will be times when the nutritional state may be optimal and other times it is sub-optimal. Treatment in this manner can lead, more often over long than short periods of time, to an inadequate nutritional state, so that relapse is prone to occur. One would not consider it a suitable preventive measure because a child did not like food rich in vitamin C to only once a month force the child to take a large amount of such food. A recurrent state of partial vitamin C deficiency would exist without perhaps ever, or at least for a long time, the development of the outspoken signs of scurvy. One must, therefore, plan for maintenance treatment to be regular and frequent. Daily treatment for pernicious anemia seems to be the ideal, but it is probably satisfactory for potent material to be given intramuscularly every two to four days, so long as an optimal amount for the given case is administered. It seems unwise, at least in a large number of cases, for the individual to receive his supply of the active principle at much longer intervals.

There is not sufficient knowledge to stipulate precisely the different amounts of material of many different sorts required for the multiple variety of states that may occur in pernicious anemia. The object has been to indicate the importance of recognizing that this disease should be treated on a quantitative basis, like any other condition due to a deficiency. It is obviously evident that it is a great deal better to give too much potent material than one bit too little. The use of "customary doses" or assumed optimal quantities will lead to unsatisfactory results. Each case should be considered as an individual problem and it must be appreciated that two cases may appear to be of the same severity, but that one will be found to require much more potent material than the other, even when given parenterally. Failure implies an incorrect diagnosis, or an inadequate amount of a potent preparation entering the appropriate organs of the body, or serious complication often capable in itself of causing death. The object is not to make the patient simply better, but to give him the very best possible health by supplying potent material

to meet the optimal daily demands of the body for life. In doing so, accessory treatment must be carried out carefully, for if this is improperly done the best results will not be obtained from the treatment of any deficient state on a quantitative basis.

SUMMARY.

Pernicious anemia, like other deficient states, should be treated on a quantitative basis by supplying enough potent material to meet the optimal daily demands of the given patient's body throughout life. To give enough just to maintain the red blood cells at their normal numbers does not imply that all demands of the body have been met adequately. Parenteral therapy readily permits any patient to receive an optimal quantity of potent material for his given case, although for the usual case it is simple to administer a suitable amount by mouth.

BIBLIOGRAPHY.

1. CASTLE, W. B., HEATH, C. W., and STRAUSS, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. IV. A Biologic Assay of the Gastric Secretion of Patients with Pernicious Anemia having Free Hydrochloric Acid and that of Patients without Anemia or with Hypochromic Anemia having no Free Hydrochloric Acid, and the Rôle of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia. *Am. Jour. Med. Sci.*, 182:741, (Dec.) 1931.
2. STRAUSS, M. B., TAYLOR, F. H. L., and CASTLE, W. B.: Intramuscular Use of Liver Extract:—Maximal Responses of Reticulocytes from Daily Intramuscular Injections of Extract Derived from Ten Grams of Liver: Preliminary Communication. *Jour. Am. Med. Assoc.*, 97:313, (Aug. 1) 1931.
3. COHN, E. J., MINOT, G. R., ALLES, G. A. and SALTER, W. T.: The Nature of the Material in Liver Effective in Pernicious Anemia. II. *Jour. Biol. Chem.*, 77:325, (May) 1928.

DISCUSSION.

DR. WALTER A. BAETJER: When Dr. Hamman asked me if I would discuss Dr. Minot's paper, he very aptly said that discussion would be limited to two minutes, which I thought was fine, because I didn't see any possible chance of requiring two minutes of my time to attempt to add anything to what Dr. Minot possibly would say on this subject. When a person presents a paper who knows all about a subject, like Dr. Minot, he really leaves a discussor just two possibilities: One is to ask questions, or else just to say, "Me, too," and discuss it in two words rather than two minutes.

Therefore I am going to ask Dr. Minot a question or two and use my time up in that way, but before doing that I should like to say what struck me most

forcibly in Dr. Minot's paper. It is so rare when one more or less specializes in a subject that he does not get so arbitrary about it as to lay down a law just as though it applied to the universe, forgetting the fact that there is much of individuality still left in patients.

For example, we have seen this done in various branches of medicine. The syphilologist tells you how much arsenic must be given, and how many years you must give it arbitrarily, no matter what your reactions are. The cardiologists in recent years have told us, "You must give digitalis according to so much per kilo of body weight." We have strayed away from that. The syphilologist now knows that arsenic is required by different patients in differing quantities for differing periods of time. Even the diabetic specialists now recognize that the way the patient feels is sometimes more important than just having his urine free from sugar, and that oftentimes it does not pay to sacrifice physical health, strength and weight for a trace of sugar if you have to do too much to avoid that.

Dr. Minot impressed more than anything else on me, rather than just the talk on pernicious anemia, which we all could follow because it was so simply and so clearly given, the fact that he does not fail to recognize an underlying clinical law, namely, that you cannot standardize human beings by a yardstick in any particular line or in any particular therapy.

He has called attention to a point, not just in these words, which I think we are all inclined to overlook, namely, that in blood, as in almost everything else, there is a tremendous body reserve which also must be built up. When a person is treated for pernicious anemia and starts with a million and a half red blood cells, and you raise that to five million cells, you still have not finished your job until you have gotten that patient to the point where at least theoretically you have put back the reserve that he started with. Even if you get a reticulocyte response, you still have not finished the job until you have gotten to the point where the reserve has been built up.

To my mind those were the important points that Dr. Minot pointed out and with which I can only heartily concur.

PRESIDENT HAMMAN: Dr. Minot's paper is now open for general discussion. Are there any further comments on this paper?

DR. ROY ROSS SNOWDEN: I was particularly impressed by Dr. Minot's emphasis that pernicious anemia is not only a disease of the blood, but also involves other systems, such as the nervous and the gastrointestinal.

We are very apt to forget these other two systems when treating these patients from the strictly clinical standpoint. In trying to emphasize this fact to students I have adopted this striking analogy, namely, that it is very unfortunate that the blood picture responds so promptly to the treatment of liver. If it were slower in response it would then be somewhat in parallel with the central nerve degeneration and gastrointestinal symptoms, and the treatment would be pushed until all of these three involved systems were adequately treated. It is not uncommon at all that the patient's blood has been returned to

practically normal, yet the patient will continue to suffer from vague gastrointestinal disorder symptoms and is very much dissatisfied, feeling that the diagnosis must be incorrect, and the physician, if he does not realize the importance of continuing the intensive treatment may, himself, begin to feel that some other condition is present. I feel that we should especially emphasize to the patient and in our own minds the importance of pushing the treatment until all of the three systems have been adequately restored to normal.